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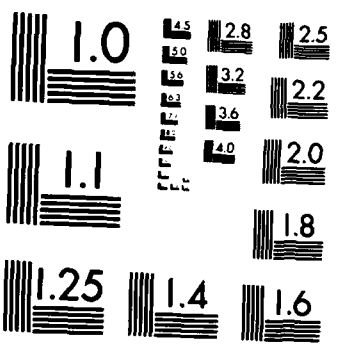

UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010-5422

PRELIMINARY ASSESSMENT OF THE RELATIVE TOXICITY OF
AI3-20827 IN ANIMALS
STUDY NO. 75-51-0529-86
MARCH 1985 - JULY 1986

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO ATTENTION OF

HSHB-MO-T

19 September 1986

SUBJECT: Preliminary Assessment of the Relative Toxicity of AI3-20827 in Animals, Study No. 75-51-0529-86, March 1985 - July 1986

Executive Director
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20307-5001

EXECUTIVE SUMMARY

The purpose and a summary of the recommendations of the enclosed report follow:

a. Purpose. To provide preliminary toxicity data for the candidate cockroach repellent AI3-20827. These data are intended to provide guidance in selecting compounds for further entomological and toxicological evaluation. In addition, the data may be useful in developing preliminary safety guidelines for handling this compound.

b. Recommendations. Based on professional scientific judgment, the following recommendations are offered.

(1) AI3-20827 should be considered for more extensive entomological and toxicological testing.

(2) Personnel handling this compound should avoid contact with the skin and eyes. In case of contact, the area should be flushed with plenty of water.

FOR THE COMMANDER:

Encl

Walter G. Peterstems
For N. JOE THOMPSON
Colonel, MC
Director, Occupational and Environmental Health

CF:
HQDA(DASG-PSP) (wo/encl)
Comdt, AHS (HSHA-IPM) (w/encl)
Dir, Advisory Cen on Tox, NRC (2 cy) (w/encl)
USDA, ARS (Dr. Terrence McGovern) (w/encl)
USDA, ARS - Southern Region (w/encl)
Cdr, USMRDC (SGRD-DPM/COL Reinert) (w/encl)

DEPARTMENT OF THE ARMY
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PRELIMINARY ASSESSMENT OF THE RELATIVE TOXICITY OF AI3-20827 IN ANIMALS
STUDY NO. 75-51-0529-86
MARCH 1985 - JULY 1986

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man and Animals Research Laboratory, Gainesville, Florida, 5 December 1984.

b. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army, Office of The Surgeon General; the Armed Forces Pest Control Board and the Department of Agriculture, Agricultural Research, Science and Education Administration; titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCES.

a. Guide for the Care and Use of Laboratory Animals, US Department of Health and Human Services, NIH Publication No. 86-23, revised 1986.

b. Topical Hazard Evaluation Program Procedure Guide, Toxicology Division, US Army Environmental Hygiene Agency (USAEHA), October 1985.

c. Standing Operating Procedures of the Toxicology Division, USAEHA.

d. Final Report, Mutagenicity Evaluation of AI3-20827F in the Ames Salmonella/Microsome Reverse Mutation Assay, Hazleton Biotechnologies Company, HBC Project No. 20988, May 1986.

3. PURPOSE. The purpose of this report is to provide preliminary toxicity data for the candidate cockroach repellent AI3-20827. This report summarizes the toxicological data for USDA candidate cockroach repellent AI3-20827. These data are intended to be used in selecting compounds for more extensive entomological and toxicological testing. The data may also be used in establishing preliminary safety guidelines for handling the material. Key words: Skin irritation; Rabbits; Rats; Inhalation; Rat

Use of company names does not imply endorsement by the US Army, but is intended only to assist in identification of a specific product.

4. BACKGROUND.

a. General. The preliminary toxicological evaluation of candidate cockroach repellents consists of a series of acute screening tests designed to assess potential hazards from single exposures by various routes of administration. The test battery included:

(1) Rat oral approximate lethal dose (ALD).

(2) Primary irritation (skin and eye).

(3) Dermal sensitization.

(4) Saturated vapor (inhalation hazard).

(5) Physiological screen.

(6) Mutagenicity (Ames test).

b. Project Information.

(1) All raw data from this study may be found in project file number 75-51-0529-86 or USAEHA Laboratory Notebooks Numbered 101 and 106.

(2) In conducting the studies described in this report, the investigators adhered to reference 2a. In addition, these studies were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

5. PROCEDURES.

a. Test Compound. Two lots (e and f) of AI3-20827 were synthesized and supplied for use in the toxicological evaluations by Dr. Terrance McGovern, USDA, Beltsville, Maryland. AI3-20827 is a clear oily liquid with a sweet odor. It exhibits low solubility in water but is soluble in acetone and other organic solvents. It has a molecular weight of 211 and a boiling point of 103°C at 0.2 mm Hg.

b. Methods.

(1) Acute Toxicity Tests. Detailed descriptions of the methodology for tests (a) through (d) listed below are published in reference 2b. Methodology for test (e) is published in reference 2c.

(a) Rat ALD.

(b) Skin irritancy.

(c) Eye irritancy.

(d) Dermal sensitization (Buehler technique).

(e) Saturated vapor.

(2) Mutagenicity. Mutagenicity testing was performed by Hazleton Biotechnologies Company under contract DAAD05-86-M-L723 with USAEHA. A complete description of the methodology and results may be found in the final report (reference 2d).

(3) Physiological Screening. The physiological screening tests were designed to obtain basic information on the underlying mechanisms of action for this compound. Male Sprauge Dawley rats, weighing between 270 - 380 g, were anesthetized with sodium pentabarbital (30 mg/kg). A heparinized cannula (15 cm length of PE50 tubing) was inserted into the left carotid artery for blood pressure monitoring. A similar catheter was inserted into the right external jugular vein for drug injection. A Statham P23-AC fluid-filled pressure transducer (Gould instrument) was used for blood pressure monitoring. The signals were processed by a Buxco Model 6 Pulmonary Function Analyzer (Buxco Electronics) and printed on a Texas Instruments Silent 700 terminal. EKG's were monitored from LEAD II and fed through a pre-amplifier and Buxco EKG analyzer. A digital recording of wave heights and intervals was printed on a second Texas Instruments TI terminal. Following a short period of time, usually 10-15 minutes, stable physiological recordings were obtained and the animals were treated with challenge doses of standard pharmacological drugs including epinephrine, norepinephrine, acetylcholine and histamine. Saline injections served as a volume control. Preliminary experiments were performed in order to find optimum dosage levels. In most cases, the dosage chosen produced a marked change in blood pressure (10-50 mm Hg) lasting less than 5 minutes. Following the initial drug challenges, the test compound AI3-20827 was injected intraperitoneally, and the drug challenges were repeated 15 minutes post injection. For each drug, the maximum change from baseline condition was recorded and the pre- and post-dosing values compared. In this way, each animal served as its own control. The data were analyzed using a two-way analysis of variance with repeated measures program on an IBM PC microcomputer. A least-significant range test was used to compare pre- and post-dosing values. A probability of less than 0.05 was used as the level of significance.

6. RESULTS.

a. ALD. The rat oral ALD was found to be $\geq$5000 mg/kg. This was the only dose that proved lethal. With the exception of the lowest dose tested (293 mg/kg) all animals exhibited marked salivation minutes after dosing.

b. Skin Irritation. AI3-20827 was found to be a category IV or moderate to severe skin irritant in the Draize rabbit skin test (see Appendix B for a description of the scoring system). Heavy plaques and eschars were observed 2-3 days post application. There was little or no difference between intact and abraded skin.

c. Eye Irritation. Based on our Draize eye test in rabbits, this compound is a mild eye irritant. It produced injury to both cornea and conjunctiva; however, in all cases, the injury was healed by 7 days post application. Washing the eyes with water immediately post application reduced the eye injury as well as the healing time.

d. Skin Sensitization. Challenge doses of AI3-20827 did not produce a reaction in pretreated guinea pigs and, based on these data, it is not considered to be a sensitizer.

e. Saturated Vapor. As indicated in Table A-1 (Appendix A), exposure to atmospheres of AI3-20827 for 8 hours did not produce any mortalities during the exposure or for up to 14 days post exposure. Nominal chamber concentrations, based on amount of material volatilized, were 0 and 4.23 mg/L for the 22 °C and 100 °C bubblers, respectively. Rats exposed to the higher concentration exhibited excessive salivation and rapid breathing, suggesting that the compound is a respiratory irritant. Twenty-four hours post exposure, these animals appeared normal. Table A-2 (Appendix A) presents the body weight gain and organ-to-body weight ratios from this experiment. There were no significant differences in any of these parameters between the exposure groups.

f. Physiological Studies. Table A-3 (Appendix A) illustrates the cardiovascular effects of exposure to sublethal intraperitoneal injections of AI3-20827. The values presented represent the maximum change from resting or baseline levels in response to injections of the challenge drug. Overall, the compound treated rats exhibited a reduced blood pressure response to the challenge drugs; however, this was only statistically significant in the case of norepinephrine. AI3-20827 did produce a marked, statistically significant decrease in resting blood pressure.

g. Mutagenicity. AI3-20827 did not exhibit mutagenic activity under the test conditions employed. It was negative in all test strains used (Salmonella typhimurium strains TA-1535, TA-1537, TA-1538, TA-98 and TA-100) and at dosages ranging from 0.1 µL to 25 µL per plate both activated and nonactivated test systems (reference 2d).

7. CONCLUSIONS. Compound AI3-20827 is moderately toxic by the oral route of exposure. It is a mild eye irritant and a moderate to severe skin irritant. This compound presents no acute inhalation hazard at room temperatures though at higher temperatures or if the repellent is atomized as an aerosol, it may cause skin, eye and respiratory irritation. We found no indication of a sensitization reaction and it was not mutagenic in the Ames test. When administered at approximately 0.5 x the ALD to anesthetized, catherized rats, it did significantly decrease baseline mean blood pressure and there was a trend toward reduced blood pressure responsiveness to pharmacological drug challenges.

8. RECOMMENDATIONS. The following recommendations are based on professional scientific judgment.

a. AI3-20827 should be considered for more extensive entomological and toxicological testing. Toxicological tests should include a more detailed evaluation of acute toxicity by multiple routes of administration, an assessment of the effects of repeated dosing and a complete evaluation of mutagenic potential.

b. Personnel handling this compound should avoid contact with skin and eyes. In case of accidental contact, the area should be flushed with plenty of water.

9. ACKNOWLEDGMENT. The project personnel shown in Appendix C assisted in the experiments.

Glenn J. Leach

GLENN J. LEACH
Biologist
Toxicology Division

APPROVED:

Maurice H. Weeks

MAURICE H. WEEKS
Chief, Toxicology Division

APPENDIX A

RESULTS

TABLE A-1. SUMMARY OF TOXICITY DATA CANDIDATE COCKROACH REPELLENT AI3-20827

ALD (Mg/Kg)	Skin Category	Eye Category	Sensitization	Sat Vapor	Physio	Ames
≥5000	IV	C	Negative	No deaths, High conc-irritant	decreased blood pressure	Negative

NOTE: See Appendix B for SOP's to explain skin and eye scoring system.

TABLE A-2. SUMMARY OF SATURATED VAPOR DATA COMPOUND AI3-20827

Parameter/ Test Group	Body Wt	Liver Wt_{x100} Body Wt	Kidney Wt_{x100} Body Wt	Heart Wt_{x100} Body Wt	Lung Wt_{x100} Body Wt	Testes Wt_{x100} Body Wt	Brain Wt_{x100} Body Wt	Spleen Wt_{x100} Body Wt
Control	233 ± 0.003	6.099 ± 0.205	1.114 ± 0.047	0.415 ± 0.016	0.649 ± 0.010	0.995 ± 0.020	0.786 ± 0.014	0.432 ± 0.015
Low Temp	239 ± 0.005	6.688 ± 0.344	1.174 ± 0.022	0.451 ± 0.009	0.644 ± 0.029	0.901 ± 0.012	0.767 ± 0.016	0.412 ± 0.043
High Temp	228 ± 0.004	6.032 ± 0.182	1.153 ± 0.035	0.453 ± 0.009	0.690 ± 0.040	0.974 ± 0.023	0.793 ± 0.013	0.436 ± 0.041

Body weight and organ to body weight ratios, saturated vapor experiment, compound AI3-20827. Numbers represent the mean ± standard error of the mean for six animals. There were no statistically significant differences among the three groups for any of these parameters.

TABLE A-3. SUMMARY OF CARDIOVASCULAR RESPONSES TO AI3-20827

	Blood Pressure		Heart Rate		QRS Width		QT Interval		P Width		R Width		P Height		R Height	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
EPI	175 ± 3	168 ± 5	254 ± 70	377 ± 31	32 ± 2	29 ± 1	60 ± 1	63 ± 1	13 ± 2	20 ± 2	16 ± 1	16 ± 3	0.22 ± 0.17	0.13 ± 0.03	13.40 ± 3.47	20.20 ± 2.52
ACH	66 ± 16	76 ± 4	414 ± 28	380 ± 26	30 ± 4	28 ± 2	59 ± 2	61 ± 1	17 ± 1	20 ± 1	18 ± 4	15 ± 2	0.15 ± 0.07	0.11 ± 0.01	17.00 ± 1.26	20.20 ± 1.36
NE	174 ± 3	40 ± 6*	322 ± 72	427 ± 23	28 ± 2	28 ± 2	61 ± 2	60 ± 2	19 ± 1	21 ± 1	14 ± 2	13 ± 1	0.11 ± 0.01	0.15 ± 0.02	18.60 ± 2.01	21.20 ± 1.66
HIST	101 ± 10	89 ± 3	408 ± 18	363 ± 35	28 ± 2	29 ± 2	61 ± 2	62 ± 1	19 ± 1	20 ± 1	14 ± 1	14 ± 1	0.13 ± 0.02	0.14 ± 0.02	18.80 ± 1.98	20.00 ± 1.87
SAL	135 ± 6	99 ± 4*	402 ± 18	400 ± 32	27 ± 2	26 ± 2	58 ± 2	59 ± 1	20 ± 1	20 ± 1	12 ± 1	12 ± 1	0.13 ± 0.02	0.14 ± 0.02	20.20 ± 2.20	20.40 ± 1.72

Values presented represent the mean ± standard error of the mean for five animals. Maximum change in reponse to drug challenge were recorded. Data were analyzed with a two way analysis of variance for repeated values and the least significant range post hoc test. * indicates significantly different from pre-exposure values $p \leq 0.05$. Drug abbreviations are as follows: EPI - epinephrine, ACH - acetylcholine, NE - norepinephrine, HIST - histamine, SAL - saline.

Study No. 75-51-0529-86, March 1985 - July 1986

APPENDIX B

DEFINITIONS OF CATEGORIES OF SKIN AND EYE IRRITANTS

1. SKIN IRRITANTS.

a. Category I - Compounds producing no irritation of intact skin or no greater than mild primary irritation of the skin surrounding an abrasion.

b. Category II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion.

c. Category III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion.

d. Category IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and in addition, producing necrosis, vesiculation, and/or eschars.

e. Category V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound.

2. EYE IRRITANTS.

a. Category A - Compounds noninjurious to the eye.

b. Category B - Compounds producing mild injury to the cornea.

c. Category C - Compounds producing mild injury to the cornea and in addition some injury to the conjunctiva.

d. Category D - Compounds producing moderate injury to the cornea.

e. Category E - Compounds producing moderate injury to the cornea and in addition, some injury to the conjunctiva.

f. Category F - Compounds producing severe injury to the cornea and to the conjunctiva.

APPENDIX C

PROJECT PERSONNEL

The experiments described in this report were performed by a multidisciplinary group under the direction of Glenn Leach. The group included the following:

1. SGT Lynn M. Balczewski, USA.
2. John G. Harvey, Bio Lab Tech.
3. John T. Houpt, Bio Lab Tech.
4. CPT R. David Russell, VC.

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